IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.	:	10/564,674
Applicants	:	MARCEL WIJLAARS et al.
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Title	:	TISSUE SUBSTITUTE MATERIAL
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Commissioner for Patents
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DECLARATION UNDER 37 C.F.R. §1.132

I, **Jacques Marie René Jan Huyghe** declare as follows:

1. I am a citizen of the Netherlands and reside at Sijsjesstraat 3, 2340 Beerse. I graduated from Ghent University (Belgium) in 1979 and received a Master's degree in Civil Engineering. I obtained a Ph.D. degree from Eindhoven University of Technology (The Netherlands) in 1986. I have had 30 years of experience within the field of Biomechanics and Mechanics of Materials, working for the Belgian Ministry of Defense, University of Twente (The Netherlands), Eindhoven University of Technology (The Netherlands) and Maastricht University (The Netherlands). Additionally, I am the author of the publications related to the field of biomechanics, engineering mechanics and prosthesis design and indexed in Exhibit A which is attached hereto. I am also one of the inventors of the subject-matter for which US 10/564,674 is filed.

2. I have read and am thoroughly familiar with the contents of the above-identified patent application. Furthermore, I have read and understand the Office Actions issued by the United States Patent and Trademark Office on March 28, 2008 and December 8, 2008 and the issues and prior art references listed therein, specifically Malmonge et al. (Artificial Organs 2000, 24:174-178) (hereinafter "Malmonge"), Pissis et al. (Proceedings of the 10th International Symposium on Electrets 1999 p. 561-564) (hereinafter "Pissis"), Young et al. (Biomaterials 1998: 1745-1752) (hereinafter "Young") and Kou et al. (Journal of Controlled Release 1990 12:241-250) (hereinafter "Kou").

3.

The invention concerns a material for cartilage-like material substitution, comprising a fiber-reinforced polymerized hydrogel, wherein said polymerized hydrogel contains 10-70% (m/m) swellable fibers (based on the dry matter), wherein the length of the fibers is at least a millimeter, and wherein 1-5% (m/m) (based on the dry matter) of a substance that contains ionized groups has been added-to said polymerized hydrogel.

4.

As an expert in the field of Biomechanics and Mechanics of Materials, it is my opinion based on the disclosure of Malmonge in view of Pissis and Young, that claim 8-9 and 12-14 would

not have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter of claims 8-9 and 12-14 pertains.

In my opinion, any combination of the teachings of Malmonge, Pissis and Young would not result in a material suitable for cartilage-like material substitution, comprising a fiber-reinforced polymerized hydrogel, wherein said polymerized hydrogel contains 10-70% (m/m) swellable fibers (based on the dry matter), wherein the length of the fibers is at least a millimeter, and wherein 1-5% (m/m) (based on the dry matter) of a substance that contains ionized groups has been added-to said polymerized hydrogel, for the reasons set forth below.

5.

Malmonge describes a copolymer of 2-hydroxyethyl methacrylate (HEMA) and acrylic acid (AA) as artificial articular cartilage material. Acrylic acid ionizes into acrylate and Na^+, which is believed to result in swelling of the HEMA-AA copolymer and to contribute to the compressive strength of the cartilage material (page 175, column 1, paragraph 1). Malmonge is solely concerned with mechano-electrical transduction of the HEMA-AA copolymer and its dependence on acrylic acid content of the copolymer. Malmonge nowhere addresses the problem of providing adequate strength and tougher mechanical properties to the hydrogel.

6.

Pissis is directed towards the dielectric and water sorption properties (see title and Introduction, final sentence) of a poly(hydroxyethyl acrylate) (pHEA) gel reinforced with Nylon nanoparticles, prepared by a tedious procedure of cutting, boiling in strong acid and ultra-sonification of what once used to be fibers (Experimental, lines 8-14).
Pissis is not at all concerned with further improving the toughness of the gels; hence, there are no pointers in Pissis for applying millimeter or greater sized fibers.

Furthermore, in the nanoparticle-reinforced hydrogel according to Pissis swelling due to water sorption is confined to the PHEA hydrogel phase, and does not affect the nylon nanoparticles (see page 563, final 3 sentences); this stands in contrast to the claimed invention, wherein the fibers by itself are swellable (claim 8) and wherein a considerable volume increase can be achieved by penetration of aqueous monomer solution into the fiber prior to polymerization (see page 2, paragraph 2 and Exhibit C).

7. (added paragraph w.r.t. template Webb)

Young describes an artificial skin substitute material for wound dressing usage (Introduction, final sentence) consisting of a 2-hydroxyethyl methacrylate (HEMA) polymer hydrogel reinforced with woven or knitted nylon and elastic spandex fibers, gauzes and low lint wipers. The flat and smooth artificial skin substitute materials according to Young are characterized by being ultrathin (0.23 mm or thinner) and containing very small amounts (< 1.66 wt%) of fiber. Inherent to its intended use as wound dressing, there is no mention of the compressive properties of the reinforced hydrogel membrane according to Young.

8.

The success of the claimed invention is demonstrated in Exhibit B, where a fiber-reinforced hydrogel network is compared to a reference hydrogel network. Both samples are equilibrated with a physiological salt concentration, i.e. concentration of sodium chloride of the external bath in which the samples are equilibrated at 0.15 moles/l. After equilibration, the samples have sizes in the order of 1 cm and are tested under compression in a high humidity environment. It is shown in the attached exhibit B that the use of swellable fibers in a gel sample improves the toughness of the gel under compression. Brittle fracture can be avoided using the swellable fibers in the gel. Only minor damage is observed on the surface of the fiber-reinforced hydrogel (picture in the lower left of Exhibit B). The integrity of the sample is not affected by this minor damage. The brittle fracture seen for the non-reinforced hydrogel destroys the integrity and load-bearing capacity of the gel (picture in lower right of Exhibit B).

9.

Malmonge nowhere addresses the problem of providing adequate strength and tougher mechanical properties to the hydrogel and, as such, does not teach or suggest to include any additional material, let alone millimeter or greater sized fibers, in the polymer gel.

Although Pissis does describe the reinforcement of a polymer gel network, its solution is to provide the network with a dispersion of nanometer-sized Nylon particles. Pissis is not at all concerned with further improving the toughness of the gels; hence, there are no pointers in Pissis for applying millimeter or greater sized fibers. Therefore, the combination of Malmonge and Pissis does not yield the claimed fiber-reinforced polymerized hydrogel for artificial cartilage. Even if erroneously interpreting the term "particles" in Pissis to mean "fibers", the dimensions of the particles in Pissis [page 1 line 10 from the bottom ("*… a fine suspension of Nylon nanoparticles in water …*")] differ from the claimed fibers by a factor 1,000,000.

Moreover, Pissis teaches away from adjusting the length scales of the Nylon nanoparticles or to increase their concentration to above 10 wt% in order to prevent any agglomeration (page 561, final sentence: *"The maximum weight percentage of nanoparticles in the hydrogel that could be thus obtained was 10%; above this value the nanoparticles tend to agglomerate and their water suspension resulted in a gel-like paste which makes it unsuitable for mixing with the monomer mixture").*

Young is concerned with an artificial skin substitute material for advanced wound dressing usage. Accordingly, Young solely discloses smooth, essentially two-dimensional ultrathin woven or knitted (see Abstract) hydrogels, for which elastic strain rather than compressive strength is a prerequisite. Since the invention is concerned with artificial cartilage material, which is generally characterized by a thickness of at least 1, preferably at least 2 mm, there are no pointers for consulting Young, let alone combining the teachings of Young with the prior art.

Nonetheless, even if the skilled person would consider Pissis and/or Young, he would not arrive at the claimed invention. Instead, he would at most come up with a composite comprising very small amounts (<10 wt%, Pissis; <1.66 wt%, Young) of nanometer-sized particles (Pissis) or flat, ultrathin (< 0.23 mm) woven or knitted nylon or spandex fibers (Young). Such a composite would much more resemble the non-fiber-reinforced reference sample of Exhibit B and its compressive strength. In this respect, any reasoning leading to other forms of fiber reinforcement, such as those with large (> 10 wt%) amounts of millimeter-sized fibers, would reflect impermissible hindsight bias.

10. Additionally, as an expert in the field of Biomechanics and Mechanics of Materials, it is my opinion based on the disclosure of Malmonge in view of Pissis and Kou, that claims 8 and 10 would not have been obvious at the time the invention was made to a person having ordinary skill in the art to which the subject matter of claims 8 and 10 pertains.

11.

Kou is concerned with the mechanism of drug release from methacrylate-methacrylic acid polymer hydrogels. No mention of possible applications as cartilage substitute material is made. Kou nowhere addresses the problem of improving the toughness of such gels, let alone that it suggests reinforcement with long fibers for solving this problem.

12.

Exhibit C shows the swelling of a fiber in a monomer solution of pHEMA as visualized under a light microscope. A Lycra™ fiber (Dupont de Nemours) 17 dtex is submersed in a monomer solution of HEMA and 2 % of methacrylate, prior to the addition of initiator. This fiber has the ability of a surprisingly high-strength bonding with the pHEMA-gel with added methacrylate. The fiber is observed using light microscopy. In a short time the Lycra™ fiber increases its diameter by factor of more than 3. The length of the fiber is increased as well (not shown on the picture), although not in the same proportion as the diameter. The increase in diameter indicates a dramatic increase in volume, which can only by explained by imbibition of monomer solution. The subsequent polymerization after initiation of the chain reaction is expected to occur through the monomer-soaked fibers. This creates the observed high strength bonding between polymer fiber and gel, resulting in improved mechanical and elastic properties of the hydrogel.

13.

Although Malmonge is directed to providing an artificial articular cartilage material, it nowhere addresses the problem of providing adequate strength and tougher mechanical properties to the hydrogel; accordingly, it never suggests to include relatively large, swellable fibers in amounts of 10-70 wt% in the polymer gel.

Likewise, Kou nowhere addresses the problem of improving the toughness of polymer hydrogels, not to mention suggesting reinforcement with long, monomer soaked fibers for solving this problem.

As discussed above, Pissis describes a polymer gel network reinforced with a dispersion of nanometer-sized Nylon particles, which do not display any appreciable swelling in solution. Pissis is not at all concerned with further improving the toughness of the gels; hence, there are no pointers in Pissis for applying millimeter or greater sized swellable fibers for attaining this effect. At most, Pissis teaches the use of comminuted Nylon particles in concentrations not exceeding 10 wt%.

The invention teaches soaking up of the monomer solution into the fiber, as demonstrated in exhibit C, followed by polymerization of said monomers. As a result, polymers are formed straight through the long fiber molecules, providing a particularly robust bonding of the fiber to the polymer gel matrix. According to this procedure, improved anchoring of the reinforcing in material and toughness is obtained.

By contrast, since the hydrogel according to Pissis is prepared by polymerizing a watery suspension of Nylon nanoparticles and a mixture of monomer + crosslinker + initiator, a weight percentage of 10% at maximum of said nanoparticles in the gel can be attained before undesired agglomeration occurs (page 561, final sentence). Evidently, no soaking of monomer solution into these nanoparticles occurs. As such, Pissis clearly teaches away from the transverse polymerization of monomer-soaked fibers, in which agglomeration is not an issue and, accordingly, much more fiber (10-70% m/m) can be added.

While the Examiner plainly repeats that it would have been obvious to use the teachings of Malmonge combined with Pissis, Kou and Young, she does not provide any evidence of a teaching, suggestion or motivation therein, either explicit or implicit, for considering, let alone combining these particular references and arriving at the claimed invention. In the absence of any explanation in this respect, such mere combination of references constitutes inadmissible hindsight.

For these reasons, I respectfully submit that the invention as claimed in the instant application is non-obvious over Malmonge in view of Pissis and Young and over Malmonge in view of Pissis and Kou (and Young).

I declare further that all statements made herein of my own knowledge are true and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application and any patent issuing thereon.

Printed Name J.M.R.J. HUYGHE

Signed Name

Date 15th of May 2009

Exhibit A

1. Huyghe J.M., Oomens C.W., Campen D.H. van, Heethaar R.M. Low Reynolds number steady flow through a branching network of rigid vessels: I. A mixture theory. *Biorheology* 26, 55-71 (1989).

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Exhibit B

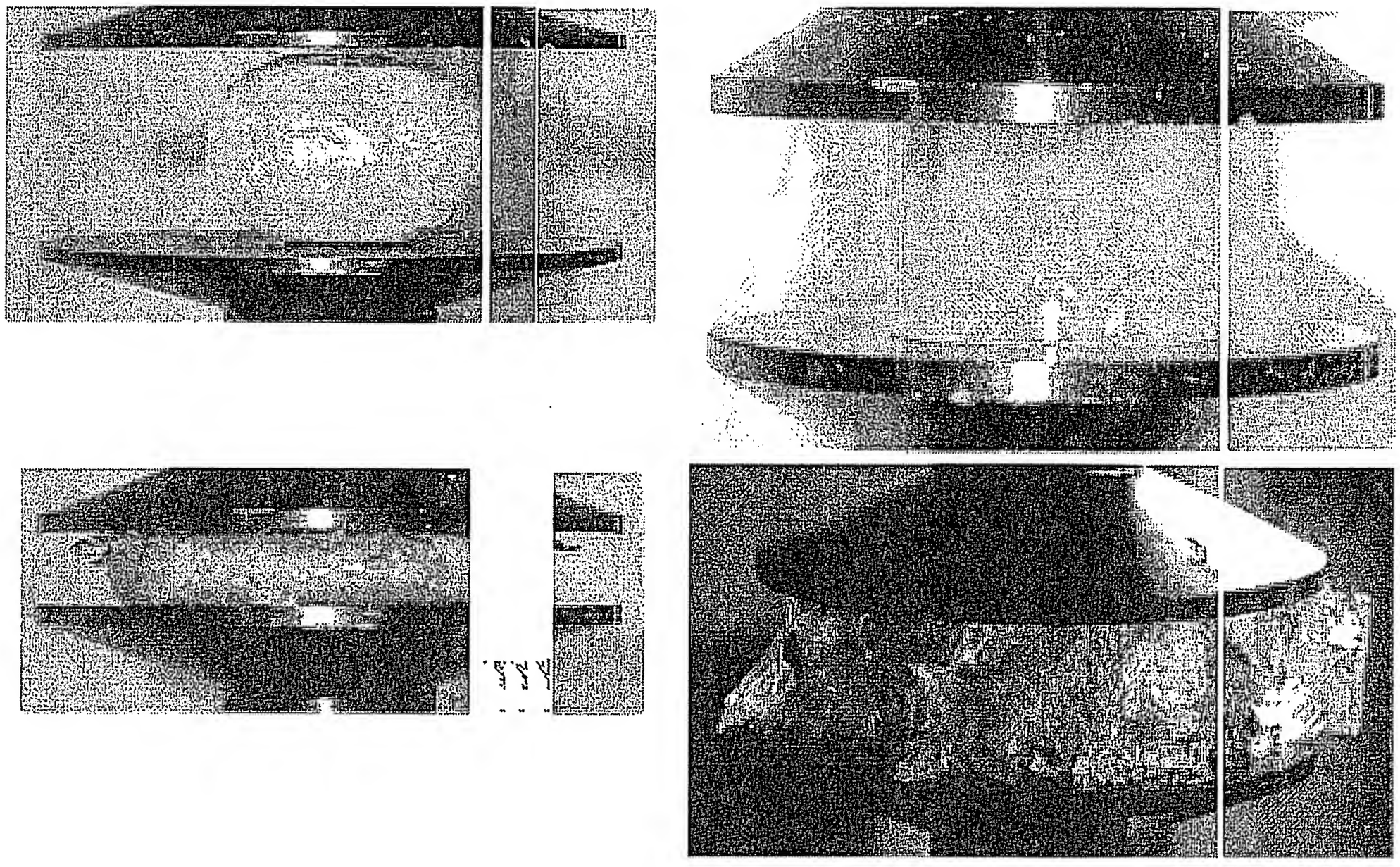

Figure: The loading of a fiber-reinforced gel (left) and a non-fiber-reinforced gel (right) shown before loading (above) and after loading (bottom). The non-fiber-reinforced gel is subject to brittle fracture (right bottom). The fiber-reinforced gel remains mostly intact after loading (left bottom).

Exhibit C

Figure: The swelling of a fiber in a monomer solution of pHEMA as visualised under a light microscope. Time runs from top to bottom. The diameter of the fiber is seen to triple in this process. The volume change is correspondingly a factor 10 higher.